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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/690,199

10/21/2003

Igor Astsaturov

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3672

7590

07/25/2006

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EXAMINER

SHEN, WU CHENG WINSTON

ART UNIT

PAPER NUMBER

1632

DATE MAILED: 07/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/690,199	Applicant(s) ASTSATUROV ET AL.	
	Examiner Wu-Cheng Winston Shen	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 May 172006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-22 is/are pending in the application.
 4a) Of the above claim(s) 2 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 3-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This application 10/690,199 filed on Oct. 21, 2003 claims benefit of provisional application 60/420,425 filed on Oct. 22, 2002. The publication number of this application 10/690,199 is US 2004/0223949 A1, published on Nov. 11, 2004.

Status of claims: Claims 1-22 are pending.

Election/Restriction

1. In response to the Restriction Requirement mailed on March 27, 2006, applicants elected with traverse the claims of Group II (claim 1 (in part), 3-7, and 8-13 (in part), and 14-22), drawn to methods of treating cancer comprising administering a nucleic acid encoding a tumor antigen and subsequently administering a cytokine, gene therapy. With respect to the species elections, applicants elected with traverse poxvirus as the vector; avipox as the poxvirus species; and gp100 as the tumor antigen species.

Applicant's election with traverse of Group II in the reply filed on May 15, 2006 is acknowledged. The traversal is on the ground(s) that a search for art related to the claims of Group I and Group II would overlap and would not cause the examiner and undue burden, and the applicants argued that this restriction be withdrawn. This is not found persuasive because polypeptide and polynucleotide are structurally and functionally distinct, and administration of each requires different considerations. Furthermore, a search for a polypeptide is not co-

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extensive with a search for a polynucleotide encoding the polypeptide and thereby presents search burdens on the examiner. This is because of the fundamental distinction in steps and technical considerations between protein therapy/vaccination and gene therapy.

Upon further consideration of prior arts, requirement of species election with respect to a poxvirus is withdrawn and species election with respect to a tumor antigen is also withdrawn.

The requirement is still deemed proper and is therefore made FINAL.

Claim 2 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 15, 2006.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Objections to Specification

2. The spacing between words of the lines of the specification, line 19 page 20 and line 10 page 30, is such as to make reading difficult. Appropriate correction is required.

Claim Rejection – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, and 3-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating melanoma in a host by direct administration to the tumor a polynucleotide encoding a tumor antigen followed by administration of a cytokine wherein said administering of the polynucleotide and cytokine result in an increased T cell response in the host relative to the T cell response that occurs following administering of the nucleic acid alone, does not reasonably provide enablement for treating any cancer wherein a polynucleotide encoding a tumor antigen is administered by any route followed by administration of any cytokine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to perform the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is

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needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The breadth of claims 1, and 3-22 encompasses treating any cancer by the administration to a host a composition containing a nucleic acid encoding a tumor antigen via any route, and subsequently any cytokine is administered to the host.

With regard to routes of administration, claimed invention encompasses a method for treating cancer comprising a) administering to a host a nucleic acid encoding any tumor antigen such that the host develops an immune response against the tumor antigen; and b) subsequently administering to the host a high dose of any cytokine (claim 1). Thus, the breadth of claim 1 and its dependent claims 3-22 encompasses any route of administration to deliver nucleic acid encoding a tumor antigen to the host for the treatment of any cancer. Practicing the claimed invention as broadly as claimed would require administration by any medically accepted means for introducing the therapeutic directly or indirectly into a subject, including but not limited to injections (e.g., intravenous, intramuscular, subcutaneous, intracranial or catheter); oral

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ingestion; intranasal or topical administration; and the like. The choice of a particular route of administration for treatment of a given cancer and a particular route of administration suitable for treatment of one type of cancer may not be applicable to the treatments of other cancers.

The specification, contemplates, for instance, “nucleic acids encoding immunogenic targets may be administered to patients by any of several available techniques” (See lines 26-27, page 25, instant application, 10/690,199), does not reasonably provide the enablement for different routes of administration. Relevant to the routes of administration issue, the specification states “Retroviral vectors may be administered by traditional methods (i.e., injection) or by implantation of a “producer cell line” in proximity to the target cell population” (See lines 17-12, page 26, instant application, 10/690,199). In the absence of specific and explicit descriptions of detailed conditions required for successful administration of a polynucleotide expressing a tumor antigen for different routes of administration for treating a given cancer, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification explicitly contemplates various routes of administration and ways of contacting the cancerous cells. However, the specification provides no guidance at all as to (1) how to direct the delivery of compositions to the intended site other than by administration directly to that site, and (2) how to establish a sustained delivery or sustained release mechanism, which can deliver the formulation internally. The claimed administration of a polynucleotide encoding a tumor antigen, for instance gp100, is a cellular protein, and it is not a diffusible product; so the nucleic acids encoding it must be delivered to the cells at sites where the protein

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is required. While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired sites has continued to be unpredictable and inefficient for the past decade. This statement is supported by numerous teachings available in the art. For example, Miller et al. (Miller and Vile, Targeted vectors for gene therapy, *FASEB J.* 9(2): 190-9, 1995) reviewed the types of vectors available for *in vivo* gene therapy, including retroviral, adenoviral, liposomal, and molecular conjugates, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (Deonarain, Ligand-targeted receptor-mediated vectors for gene delivery, *Exp. Opin. Ther. Patents* 8(1): 53-69, 1998; Ashley Publications Ltd. ISSN 1354-3776) reviewed ligand-targeted receptor mediated vectors, and indicated that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviewed techniques under experimentation in the art which showed promise, but which are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (Verma and Somia, Gene therapy -- promises, problems and prospects, *Nature* 389: 239-42, 1997) reviewed various vectors known in the art for use in gene therapy and the problems that are associated with each. Verma clearly indicated that resolution to vector targeting problems had not been achieved in the art (see entire article). Verma discussed the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239 and 2nd and 3rd column of

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page 242). Crystal (Crystal, Transfer of genes to humans: early lessons and obstacles to success, *Science* 270: 404-10, 1995) also reviewed various vectors known in the art and indicated, “among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated” (page 409). Pouton et al. (Pouton and Seymour, Key issues in non-viral gene delivery, *Adv Drug Deliv Rev.* 46(1-3): 187-203, 2001) reviewed the issues in non-viral gene delivery and stated that “direct injection of gene medicines into target tissue represents a far simpler task than targeting delivery to a specific tissue from the systemic circulation”. See last full sentence on page 188, right column, and section 2.1. Pouton et al. added that there were “no systems yet available for efficient tissue targeting following systemic delivery.” (See page 189, first sentence of section 2.2.). More recently, Read et al (Read et al., Barriers to gene delivery using synthetic vectors, *Adv Genet.* 53: 19-46, 2005) stated after the time the invention was filed that the “lack of suitable vectors for the delivery of nucleic acids... represents a major hurdle to their continued development and therapeutic application” (see abstract, sentence bridging pages 19 and 20. Problem areas included obtaining persistence in the circulation, gaining access to target cells, and distinguishing target cells from non-target cells. See e.g. page 22). Finally, Dobson (Dobson, Gene therapy progress and prospects: magnetic nanoparticle-based gene delivery. *Gene Ther.* 13(4): 283-7, 2006) reviewed the development of non-viral transfection agents for gene delivery stated “While magnetic targeting appears to hold significant potential for gene therapy, there are still major obstacles to employing this technique in the clinic. Perhaps, the problem that is most difficult to overcome is, as with magnetic targeting for drug delivery, that of scale-up.” (See Prospects on page 286).

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The specification as filed fails to teach any specific targeting techniques, fails to provide any working examples which encompass vector targeting, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art which would allow one of skill in the art to practice the claimed invention without undue experimentation. In view of the state of the art, the unpredictability in the art, and the lack of guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to practice the claimed invention in treating cancer by administering the nucleic acid sequences encoding a tumor antigen by any route other than directly to the tumor followed by a cytokine.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, and 3-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The basis of this rejection focuses on the method for “subsequently administering to the host a high dose of cytokine” stated in claim 1. The term “high dose of a cytokine” does not set forth the metes and bounds of the dose of any given cytokine encompassed by claim 1. The specification does not clearly define as to what dose will be considered a high dose of cytokine.

Claim Rejection – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 3-8, 14-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Paoletti (U.S. patent number 5,942,235; issued on August 24, 1999).

With regard to claims 1 and 3, Paoletti teaches attenuated recombinant viruses containing DNA coding for a cytokine and/or a tumor associated antigen (TAA), as well as methods and compositions employing the viruses for cancer therapy (See abstract). Paoletti also teaches that immune responses in a mammalian host against tumor cells are mediated by T-cells, particularly cytotoxic T lymphocytes (CTLs); white blood cells capable of killing tumor cells and virus-infected cells (column 7, lines 55-57). Furthermore, Paoletti teaches the administration of a cytokine secreted from modified tumor cells can subsequently be utilized for active immunization. The therapeutic potential for such an administration is based on the ability of cytokines to alter the presentation of TAAs to achieve systematic anti-tumor activity (See column 16, lines 3-8).

With regard to claims 4-8 and 14-15, Paoletti teaches (1) viral vectors including poxvirus, vaccinia virus, and avipox virus (See, for instances, column 2, background of the invention, second paragraph; claims 1-8); NYVAC, ALVAC, and TROVAC based recombinant viruses expressing TAAs plus or minus specific cytokines for adoptive immunotherapy (See column 15,

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lines 45-48, column 17, lines 8-9); as well as canarypox virus (column 16, line 55) and fowlpox virus (column 16, line 64); (2) expression of tumor antigens --- CEA, carcinoembryonic antigen, (columns 70-77, example 17); p53 (columns 65-68, example 15); MAGE-1 (columns 68-70, example 16); and cytokines --- human INF γ (columns 83-84, example 21), IL-2 (column 79-80, example 19) in both ALVAC and NYVAC based viral vectors.

Claim Rejection – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1, 9-10, and 16-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paoletti (U.S. patent number 5,942,235; issued on August 24, 1999) in view of Kirkwood et al.

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(Kirkwood et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. *J Clin Oncol.* 19(9): 2370-80, 2001).

Paoletti teaches attenuated recombinant viruses containing DNA coding for a cytokine and/or a tumor associated antigen (TAA), as well as methods and compositions employing the viruses for cancer therapy (See abstract). Paoletti also teaches that immune responses in a mammalian host against tumor cells are mediated by T-cells, particularly cytotoxic T lymphocytes (CTLs); white blood cells capable of killing tumor cells and virus-infected cells (column 7, lines 55-57). Furthermore, Paoletti teaches the administration of a cytokine secreted from modified tumor cells can subsequently be utilized for active immunization. The therapeutic potential for such an administration is based on the ability of cytokines to alter the presentation of TAAs to achieve systematic anti-tumor activity (See column 16, lines 3-8).

Paoletti also teaches (1) viral vectors including poxvirus, vaccinia virus, and avipox virus (See, for instances, column 2, background of the invention, second paragraph; claims 1-8); NYVAC, ALVAC, and TROVAC based recombinant viruses expressing TAAs plus or minus specific cytokines for adoptive immunotherapy (See column 15, lines 45-48, column 17, lines 8-9); as well as canarypox virus (column 16, line 55) and fowlpox virus (column 16, line 64); (2) expression of tumor antigens --- CEA, carcinoembryonic antigen, (columns 70-77, example 17); p53 (columns 65-68, example 15); MAGE-1 (columns 68-70, example 16); and cytokines --- human INF γ (columns 83-84, example 21), IL-2 (column 79-80, example 19) in both ALVAC and NYVAC based viral vectors.

However, Paoletti does not teach administration of high dose INF- α 2b.

With regard to claims 1, 9-10 and 16-22, Kirkwood et al. teach high dose INF- α 2b in the treatment of patients with melanoma. Specifically, Kirkwood et al. teach high dose of INF- α 2b (20 megaunits [MU]/m²/d IV (intravenously) X 5 days a week for four week and 10 MU/m² SC (subcutaneously) three times per week [TIW] X 48 weeks), which was approved as adjuvant therapy for high-risk melanoma by the United States Food and Drug Administration (FDA) in 1995 (See first paragraph of Introduction). The treatment significantly prolongs relapse-free survival and overall survival in high-risk melanoma patient. However, Kirkwood et al. do not teach combining high dose INF- α 2b cytokine therapy with expression of a tumor antigen as a potent treatment of cancers.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention to substitute the cytokine (including INF γ and IL-2) secreted from modified tumor cells by the teachings of Paoletti et al in treating cancer with a high dose INF- α 2b as taught by Kirkwood et al.

One having ordinary skill in the art would have been motivated to substitute INF γ in treating cancer by the teachings of Paoletti et al. that comprises administering to a host a composition containing a tumor antigen, subsequently administering to the host a high dose of cytokine with INF- α 2b as taught by Kirkwood et al.

There would have been a reasonable expectation of success given (1) combinatory cancer therapy with expression of a tumor antigen and subsequent administration of a cytokine (including INF γ) by the teachings of Paoletti, and (2) the results of high dose of INF- α 2b in the

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treatment of melanoma by the teachings of Kirkwood et al to achieve a tumor antigen specific immune response involving enhanced T cell response.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

7. Claims 1, 3-7 and 11-13 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Paoletti (U.S. patent number 5,942,235; issued on August 24, 1999) in view of Schlom et al. (U. S. patent number 6,045,802, issued on April 4, 2000).

Paoletti teaches attenuated recombinant viruses containing DNA coding for a cytokine and/or a tumor associated antigen (TAA), as well as methods and compositions employing the viruses for cancer therapy (See abstract). Paoletti also teaches that immune responses in a mammalian host against tumor cells are mediated by T-cells, particularly cytotoxic T lymphocytes (CTLs); white blood cells capable of killing tumor cells and virus-infected cells (column 7, lines 55-57). Furthermore, Paoletti teaches the administration of a cytokine secreted from modified tumor cells can subsequently be utilized for active immunization. The therapeutic potential for such an administration is based on the ability of cytokines to alter the presentation of TAAs to achieve systematic anti-tumor activity (See column 16, lines 3-8).

Paoletti also teaches (1) viral vectors including poxvirus, vaccinia virus, and avipox virus (See, for instances, column 2, background of the invention, second paragraph; claims 1-8); NYVAC, ALVAC, and TROVAC based recombinant viruses expressing TAAs plus or minus specific cytokines for adoptive immunotherapy (See column 15, lines 45-48, column 17, lines 8-9); as well as canarypox virus (column 16, line 55) and fowlpox virus (column 16, line 64); (2)

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expression of tumor antigens --- CEA, carcinoembryonic antigen, (columns 70-77, example 17); p53 (columns 65-68, example 15); MAGE-1 (columns 68-70, example 16); and cytokines --- human INF γ (columns 83-84, example 21), IL-2 (column 79-80, example 19) in both ALVAC and NYVAC based viral vectors.

However, Paoletti does not teach expression of tumor antigen gp100 from a viral vector.

With regard to claims 1, 3-7 and 11-13, Schlom et al. teach (1) A method of enhancing an immune response against cells expressing a tumor-associated antigen (TAA) in a mammal comprising directly infecting cells expressing a tumor-associated antigen *in vivo* with an effective amount of the composition (See claim 24), and the virus vector include but not limited to Poxvirus such as vaccinia virus, fowlpox virus and a highly attenuated vaccinia virus (MVA), adenovirus, baculovirus and the like (column 8, lines 39-42); (2) a composition comprising recombinant virus encoding a tumor-associated antigen, which includes gp100 (claims 3, 5, 7, 15, and 17); and (3) a composition comprising recombinant virus encoding a immunostimulatory molecule, which includes cytokines INF γ , IL2, IL12, and IL6 (claims 9 and 20).

However, Schlom et al. do not teach administration of a cytokine subsequent of the administration of a tumor antigen.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of invention to substitute tumor antigens (including CEA, p53) by the teachings of Paoletti in treating cancer with gp100 as taught by Schlom et al.

One having ordinary skill in the art would have been motivated to express gp100 as a tumor antigen in a host as part of a composition in the treatment of diseases such as cancer by the teachings of Schlom et al. (See abstract).

There would have been a reasonable expectation of success given (1) combinatory cancer therapy with expression of tumor antigen and subsequent administration of a cytokine (including INF γ) by the teachings of Paoletti, and (2) induction of enhanced a T-cell immune response to a human tumor associated antigen, by mixing a recombinant vaccinia virus expressing the tumor associated antigen with a recombinant vaccinia virus expressing a co-stimulatory molecule by the teachings of Schlom et al. that tumor antigen gp100 specific enhanced T-cell immune response can be achieved.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

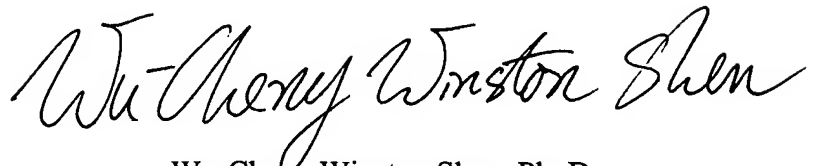
11. No claim is allowed.

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Ram Shukla, can be reached on (571) 272-0735. The fax number for TC 1600 is (571) 273-8300. Any inquiry of a general nature, formal matters or relating to the status of this

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application or proceeding should be directed to Dianiece Jacobs whose telephone number is

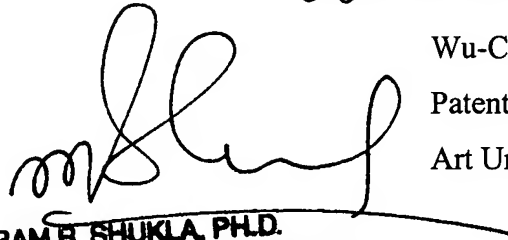
(571) 272-0532.



Wu-Cheng Winston Shen, Ph. D.

Patent Examiner

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RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER